REMARKS

Claims 1-38 and 40-44 are pending in the application. Claims 28-37 and 40-44 were withdrawn from consideration, pursuant to a Restriction Requirement. The title and claims 2-17, 22, 24, 27, and 38 were objected to, and claims 1-27 and 38 were rejected. The objections and rejections are addressed below, after a matter concerning the priority claim.

Priority Claim

The Examiner states that Applicants' claim for priority to United Kingdom application number 0315291.5, filed on June 30, 2003, is acknowledged, but benefit of the foreign filing date is not granted, because Applicants have not filed a certified copy of the foreign priority application. A certified copy of United Kingdom application number 0315291.5 is submitted today under separate cover. Applicants thus request that benefit of the priority claim to United Kingdom application number 0315291.5 be granted. Benefit of the priority claim to United Kingdom application number 0315291.5 is in addition to that to PCT/EP04/06971, which has already been granted.

Objections

The title was objected to as not being descriptive. Consistent with the suggestion of the Examiner, the title has been amended to: "Methods of determination of activation or inactivation of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) hormonal systems."

Claims 2-16 were objected to for beginning with the term "A," which the Examiner states should be replaced with "The." Claims 2-16, as well as claim 17, have been amended accordingly.

Claim 11 was objected to for failing to further limit claim 3. The Examiner states that claim 3 is drawn to a method utilizing an agent comprising SEQ ID NO:1 and SEQ ID NO:6, which are both polypeptides (Applicants have considered this statement to pertain to SEQ ID NOs:3 and 6, which are the elected species). Claim 11 specifies that the agent of claim 3 is a polypeptide. Applicants request that this rejection be withdrawn, as the agent specified in claim 3 is indicated as "comprising" the specified peptides/polypeptides, and thus is not limited to being a polypeptide. Claim 11 therefore further limits claim 3 in specifying that the agent of claim 3 is a polypeptide.

Claim 17 was objected to on the basis that the Examiner states that it would be more grammatically correct if claim 17 were amended to specify "The method according to claim 1, wherein said method is diagnostic of heart failure or monitors treatment of a heart condition." Claim 17 has been amended consistent with this suggestion.

Claim 22 was objected to for failing to further limit claim 18. The Examiner states that claim 18 is drawn to a method utilizing an agent comprising SEQ ID NO:1 and SEQ ID NO:6, which are both polypeptides (Applicants have considered this statement to pertain to SEQ ID NOs:3 and 6, which are the elected species). Claim 22 specifies that the agent of claim 18 is a polypeptide. Applicants request that this rejection be withdrawn, as the agent specified in claim 18 is indicated as "comprising" the specified peptides/polypeptides, and thus is not limited to being a polypeptide. Claim 22 therefore further limits claim 18 in specifying that the agent of claim 18 is a polypeptide.

Claims 2, 3, 9, 18, 20, 24, 27, and 38 were objected to on the basis that the Examiner states that the sequence identifiers should be amended to be in the format "SEQ ID NO:X". The claims have been amended accordingly.

Claim 38 was objected to for reciting a non-elected invention. Claim 38 has been canceled herein, without prejudice.

Rejection under 35 U.S.C. § 101

Claims 18, 19, 22-24, and 38 were rejected under 35 U.S.C. § 101 on the basis that these claims are directed to non-statutory subject matter. The Examiner states that the claims as written do not sufficiently distinguish the claimed subject matter over a polypeptide that naturally exists in an organism, because the claims do not point out any non-naturally occurring differences between the claimed sequences and naturally occurring products. Claims 23, 24, and 38 were also rejected for being directed to non-statutory subject matter, with the Examiner stating that these claims as written do not sufficiently distinguish the claimed subject matter over polynucleotides that naturally exist in an organism.

In response, Applicants note that the claimed agents are synthetic, hybrid molecules including sequences from both proANP and proBNP (or their fragments and/or homologs), as indicated in the claims. This is made clear in paragraphs [0218] – [0238] of the application publication (US 2007/0141634), which describe agents of the invention as including both proANP and proBNP-related sequences. ProANP and proBNP are encoded by different genes, and thus the claimed agents are not naturally produced. Thus, as the claimed agents, and therefore the polynucleotides that encode the agents, comprise non-naturally occurring sequences, this rejection can now be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-27 and 38 were rejected under 35 U.S.C. § 112, second paragraph, as being

indefinite on several grounds, which are addressed as follows.

Claim 1 was rejected for omitting essential elements. In particular, the Examiner states that claim 1 does not include a statement of how one is to determine if the results of the detection step indicate activation or inactivation of the ANP and BNP hormonal system, and that claim 1 does not specify what the sample is. In response, Applicants have amended claim 1 to specify that the sample is from a subject, and that detection of an increase in proANP and proBNP, or fragments thereof, in the sample indicates activation of the ANP and BNP hormonal systems, while detection of a decrease in proANP and proBNP, or fragments thereof, in the sample indicates inactivation of these systems. Support for these amendments can be found throughout the specification, for example, in paragraphs [0121], [0127], [0128], and [0135]. In view of the amendment, Applicants request that this rejection be withdrawn.

Claims 2, 3, 18, 24, 27, and 38 were rejected for utilizing the same Roman numerals in parts (a) and (b) of the claims. In particular, the Examiner notes that in claims 2, 3, 18, and 38 there are two sections identified as (iii) which refer to sections (i) and (ii), and that it is unclear which of the two different (i) and (ii) sections in the claims the references in the (iii) sections are meant to refer. This rejection has been met by the present amendments, in which any references to sections occurring in more than one part of a claim, such as section (i) as occurring in part (a) or part (b), includes an indication as to the part of the claim intended. Thus, for example, in claim 2, the references to section (i) in parts (a)(ii) and (b)(ii) of the claim have been replaced with references to sections (a)(i) and (b)(i), respectively. In view of these amendments, Applicants request that this rejection be withdrawn.

Claims 2, 4, and 38 were rejected for being indefinite in reciting "an oligospecific... binding substance" or an "oligospecific antibody," with the Examiner stating that it is unclear

whether the binding is to be to an oligonucleotide or an oligopeptide. Further, the Examiner comments that "if applicant intends to bind multiple substances, is unclear if applicant intends to utilize a substance that binds more than two substances and if so, what those substances might be, since the method is directed to detecting only two substances."

In response, Applicants first note that the claims clearly set forth the targets of the binding. In particular, claim 2 specifies that the first binding substance binds to the materials specified in parts (a) and (b) of the claim. Similarly, claim 4, in depending from claim 3, specifies that the first binding substance binds to the materials specified in parts (c) and (d) of claim 3 (as amended). The substances specified in the indicated sections comprise amino acid sequences, so it is unclear why it may be considered that the binding is to an oligonucleotide.

With respect to the possibility that Applicants may intend to cover binding to more than two substances, we note that, in reference to claim 2 as an example, as indicated by the Examiner, the first binding substance binds to a substance as specified in part (a) and part (b) of the claim. In binding to at least one substance in part (a) and one substance in part (b), it is clear that the first binding substance is at least bi-specific. However, we note that there are many related substances set forth in each part of the claim including, e.g., substances having at least 70% identity to the recited reference sequences and fragments. A first binding substance may thus be "oligospecific" if, for example, it binds to more than one of the different substances specified in part (a) and/or part (b) of the claim (and then also at least one substance from the other part of the claim). Further, a binding substance may have two or more ligand binding sites, as explained in paragraph [0186] of the application publication. In another example, the binding substance may be a bispecific antibody, which is able to bind to two different antigens, or an oligospecific antibody, which is able to bind to more than two different antigens (see paragraph

[0198] of the application publication). In view of the above, Applicants request that this rejection be reconsidered and withdrawn.

Claims 2, 3, 5, 18, 27, and 38 were rejected for being indefinite in reciting "homologous sequences," on the basis that it is unclear what properties the homologous sequences are required to retain. In response, Applicants note that paragraph [0108] of the application publication explains that variant sequences of the present invention have the same essential character as or a basic biological functionality of the sequence of which it is a variant. As stated in paragraph [0116], the "variant as referred to herein generally retains one or more of the binding characteristics of the relevant polypeptide. Alternatively or additionally, the variant may retain an antigenic activity of the polypeptide." Paragraphs [0117-0119] further describe characteristics retained, e.g., binding, antigenic properties, and generation of an immune response. Based on this, it is clear that the variants specified in the claims maintain binding and/or antigenic characteristics of the sequences of which they are variant. This rejection may therefore be withdrawn. Applicants further point the Examiner to new claim 52, which provides additional information concerning the binding characteristics of certain variant sequences.

Claim 3 was rejected for being indefinite for reciting "an agent comprising" in the third line of the claim and "(c) the agent." This rejection has been met by amendment of claim 3 to delete "(c) the agent."

Claim 7 was rejected for being indefinite in reciting "an antibody...or derivative thereof," on the basis that the metes and bounds of "derivative" cannot be determined. In response, Applicants note that the term "derivative" is generally defined as "a chemical substance related structurally to another substance and theoretically derivable from it" and " a substance that can be made from another substance." (Merriam Webster's Collegiate Dictionary, 1998). In

applying this general definition to antibodies, Applicants submit that the field of antibodies is well-developed, and that those of skill in the art would understand what is encompassed by the term "antibody derivatives." Further, this is described in paragraphs [0199] and [0200] of the application publication, where it is indicated that a derivative of an antibody encompasses antibody fragments (e.g., F(ab') and $F(ab)_2$ fragments), antibodies or fragments associated with moieties such as linkers, which may be used to join together two or more antibodies or antibody fragments, diabodies, chimeric antibodies, humanized antibodies, bifunctional antibodies, etc. Based on these passages, as well as knowledge in the art as to the many different types of well-known antibody derivatives in the art, it is clear that those of skill in the art would understand what is meant by an antibody "derivative," and Applicants therefore request reconsideration and withdrawal of this rejection.

Claim 8 was rejected for being indefinite in reciting "crossreacting polyclonal antibody," on the basis that it is unclear what the antibody is to crossreact with. In response, Applicants note that the recited term as used in the present application can refer to an antibody that recognizes distinct binding sites of an antigen that has not been used for production of the antibody. Accordingly, a crossreacting polyclonal antibody can be considered as one that recognizes a shared determinant. Moreover, a crossreacting antibody can react against one antigen, even though it was developed against another antigen. Furthermore, such an antibody can recognize two or more distinct epitopes (i.e., binding sites). Thus, a crossreacting polyclonal antibody might cross-react with fragments of proANP peptides and proBNP peptides of variable lengths.

Claim 10 was rejected for being indefinite in reciting the term "agent," on the basis that it is unclear which of the agents recited in claim 3 it is intended to indicate. This rejection can now

be withdrawn, in view of the amendment of claim 3, by which one of the references to the agent (i.e., "(c) the agent") has been removed.

Claim 13 was rejected for being indefinite in reciting "additionally comprises contacting the sample with a second binding substance..." on the basis that it is unclear at what point in the method of claim 2 the step of contacting recited in claim 13 is to be performed. In response, Applicants note that the point at which the contacting recited in step 13 is not specified, as it may be carried out at any point during the course of the method of claim 2. In an example described in the application (see, e.g., paragraphs [0156] to [0160] of the application publication), the second binding substance is added after the first binding substance. However, this order is not essential for carrying out the invention. This rejection should therefore be withdrawn.

Claim 15 was rejected for being indefinite in reciting "wherein the second binding substance causes precipitation..." on the basis that the conditions under which precipitation occurs are unclear. In response, Applicants submit that those of skill in the art have long been familiar with procedures for causing precipitation of binding substances, such as antibodies, bound to peptides. Indeed, antibody precipitation analyses have been standard in the art for decades, in order to separate bound antibodies from unbound antibodies. In reference to the present application, this concept is clearly described in paragraph [0143] of the application publication, where it is explained "the second binding substance may be a substance that causes precipitation or otherwise immobilizes and separates the first binding substance complexes." Further, an experimental example of such precipitation is provided at paragraph [0314], where it is explained that "bound and free NT-proXNP were separated by precipitation with donkey anti-goat IgG in 0.5 ml of 8% polyethylene glycol 6000, containing normal goat serum carrier (1 µl). After centrifugation, the pellet was counted for radioactivity." In view of the above, Applicants

request that this rejection be withdrawn.

Claim 16 was rejected for being indefinite, on the basis that it is unclear where in the method of claim 1 the immunoassay is performed, and that it is unclear what the immunoassay is directed to. In response, Applicants note that claim 1 specifies the simultaneous detection of proANP and proBNP (or fragments thereof) in a sample, and it is in the detection of proANP and proBNP (or their fragments) that the immunoassay specified in claim 16 is intended to be performed. Thus, the immunoassay is used in the method of claim 1 for the "simultaneous detecting" and the immunoassay is directed to proANP and proBNP (or their fragments). Applicants request that this rejection be withdrawn.

Claim 19 was rejected for being indefinite on the basis that it is not clear whether it is intended for two sequences to be present. The Examiner also states that it is unclear how the SEQ ID NOs recited in claim 20 are related to the polypeptides recited in claim 19. In response, Applicants submit that claim 19 provides that the specified agent consists of one of seven (a-g) sequences that consist of the two indicated distinct sub-sequences. Thus, in one example, the agent comprises or consists of a fusion of proBNP15-24 and proANP82-96 (a). That the sub-sequences are comprised within a single molecule is made clear in the description of agents of the invention in the application publication, such as in paragraphs [0218] – [0238]. With respect to claim 20, Applicants note that the recited SEQ ID NOs:13, 14, 15, 17, 18, 19, and 20 correspond to the fusion peptides of parts a, b, c, d, e, f, and g of claim 19, respectively. Applicants request that this rejection be withdrawn.

Claim 23 was rejected for being indefinite on the basis that claim 19 does not specify whether the agent comprises two separate proteins or a fusion protein, and thus it is not clear to what "a polypeptide" as recited in claim 23 refers. In response, Applicants note that claim 23

depends from claim 22, which depends from claim 18 (not claim 19). Claim 23 thus specifies a polynucleotide in relation to the polypeptide agent of claim 22, which is further defined by reference to claim 18. Claim 18 specifies an agent comprising a component from (a) and (b). As is made clear in paragraphs [0218] – [0238] of the application publication, agents of the invention include both proANP and proBNP-related sequences within a single molecule, so it is clear that the components in parts (a) and (b) of claim 18 are within a single molecule. Based on this, it is clear that the polypeptide of claim 23 includes within one molecule sequences from both proANP and proBNP which are, in particular, selected from the sequences listed in claim 18. In view of the above, Applicants submit that this rejection should be withdrawn.

Claim 24 was rejected for being indefinite for reciting "a sequence which hybridizes under stringent conditions..." The Examiner notes that stringent conditions may be low, medium, or high, and further that there is no required function recited for the sequences as listed in the sections other than in section (i). In response, Applicants note that claim 24 has been amended herein to specify that the hybridization takes place under medium or high stringency conditions. Support for this amendment can be found in paragraph [0255] of the application publication. With respect to function, Applicants submit that the polynucleotides of claim 24 encode binding agents, and the application makes clear how the binding agents are used in the claimed methods.

Further with respect to claim 24, the Examiner notes that the use of Roman numerals in the sections of claim 24 is confusing, as there are two lines labcled as (ii) in part (a), and there are two lines labeled as (iii) in part (b). Claim 24 has been amended herein to include only one line in part (a) labeled as (ii), and only one line in part (b) labeled as (iii).

In addition, the Examiner states that it is unclear which of the sequences "a fragment"

refers to, as there are multiple uses of Roman numerals (i) to (v). In response, Applicants note that claim 24 has been amended herein to indicate which part of the claim, (a) or (b), is being referred to when reference is made in different sections indicated by Roman numerals to other sections.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-18, 21-27, and 38 were rejected under 35 U.S.C. § 112, first paragraph for lack of enablement and lack of adequate written description. These rejections are addressed as follows.

Enablement

In the rejection for lack of enablement, the Examiner states that the specification does not enable a method comprising contacting a sample with a binding substance that is able to bind to both homologous sequences having at least 70% identity to the listed proANP and proBNP-related sequences, wherein the first binding substance is a sequence having at least 70% identity to SEQ ID NO:33 or the indicated fragments; an agent that comprises a homologous sequence having at least 70% identity to the disclosed sequences or fragments; a sequence that is complementary to or hybridizes to the disclosed sequences or fragments; or a process of producing a sequence having at least 70% identity to the disclosed sequences or fragments. Central to this rejection appears to be the fact that sequences are claimed that are at least 70% identical to reference sequences, and the Examiner's concern that those of skill in the art would not be able to determine, without undue experimentation, which portion of the sequences must be retained in order to achieve the indicated binding characteristics.

The Examiner further makes note of factors considered when determining if a disclosure

satisfies the enablement requirement, including (1) the nature of the invention, (2) the state of the prior art, (3) the relative skill of those in the art, (4) the level of predictability, (5) the existence of working examples, (6) the breadth of the claims, (7), the amount of direction or guidance provided by the inventor, and (8) the quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d, 1400, 1404 (Fed. Cir. 1988). In consideration of these factors, the Examiner concluded that the claims are not enabled because, according to the Examiner, the specification does not provide sufficient guidance as to which portions of the polypeptides must be preserved in order to maintain binding ability, which portions of the natriuretic receptor or its extracellular domain must be preserved to retain the required biological or binding activity, the lack of examples directed to assays which measure the binding of substances to polypeptide sequences having at last 70% identity to the proteins of interest, binding assays utilizing binding substances which have 70% identity to SEQ ID NO:33, etc., and the large quantity of experimentation required to determine whether the desired binding takes place. Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

Applicants first submit that the application clearly describes variants of the binding substance targets, agents, and corresponding polynucleotide sequences of the present claims, and that these variants could be made and tested using standard methods in the art (as described, e.g., in Sambrook et al., 1989). For example, pages 4-5 of the application publication provide a description of variant polypeptides, and pages 8-13 describe variant targets recognized by the first binding substance (including peptides including conserved ring structures [0179], and particular target proANP and proBNP fragments [0181]), peptide agents, and corresponding nucleic acid molecules. In reading these passages, and with knowledge of standard methods in

the art, those of skill in the art would be able to make sequences with the variant features, and to test them in assays for binding according to the methods of the invention, without undue experimentation.

As an example, and specifically regarding claim 2 and other claims including reference to proANP and proBNP related sequences (such as sequences having at least 70% identity to proANP, proBNP, and fragments thereof) to which a first binding substance binds, Applicants submit that those of skill in the art could readily prepare sequences having this level of identity, and then prepare a binding substance (such as an antibody) that binds to the sequences. Making antibodies that bind to proteins is standard in the art, and Applicants respectfully submit that undue experimentation would not be required to make such antibodies. As to using them in methods to determine activation or inactivation of ANP and BNP hormonal systems, Applicants submit that the binding substances, which bind to the homologues specified in claim 2, could readily be tested to determine whether they bind to proANP and proBNP-related sequences in samples in the same manner as binding substances directed against proANP and proBNP sequences that are naturally present in patient samples. Binding substances showing similar binding activity could thus be used in the claimed methods.

Applicants further note that, in general, activities that are relevant to the variants specified in the present claims are binding activities, such as assays for detecting binding between a binding substance, such as an antibody, and a target including particular amino acid sequences. Applicants additionally submit that it is well known in the art that identifying a binding substance that binds to a variant peptide, while perhaps requiring trial and error experimentation, is generally feasible using standard methods.

Further with respect to enablement, Applicants submit that the present rejection cannot

stand in view of *Ex Parte Kubin* (BPAI 2007). In this precedential opinion of the Board of Patent Appeals and Interferences, the Board held that a claim to an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to a reference sequence, and having a particular activity, was enabled. In consideration of the *Wands* factors in this case, the Examiner concluded that the state of the art and the relative skill in the art weighed in the applicants' favor. The Board further stated "the amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art" (citations omitted). The present case is similar to *Kubin* with respect to the claims specifying variants having a certain level of identity, the advanced state of the art, and the high level of skill in the art. Similar to the decision in *Kubin*, Applicants respectfully submit that obtaining and characterizing variants according to the present claims would have been routine. Accordingly, Applicants submit that the present claims are enabled and request that the rejection for lack of enablement be reconsidered and withdrawn. Further, to assist the Examiner in assessing the present claims, Applicants note that new claims 46-60 have been added, which provide for higher levels of identity, specify species homologues and allelic variants, and provide functional language.

Written Description

Claims 1-18, 21-27, and 38 were rejected under 35 U.S.C. § 112, first paragraph for lack of adequate written description. In making the rejection, the Examiner comments "the claims do not require that the polypeptides possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The claims do not require that the nucleic acids encode functional polypeptides." Further, the Examiner states "to provide evidence

of possession of the claimed genera, the specification must provide sufficient distinguishing identifying characteristics of the genera. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity or hybridization ability. There is not even identification of any particular portion of the structure that must be conserved." On this basis, the Examiner concludes that the claims lack adequate written description. Applicants request reconsideration and withdrawal of this rejection for the following reasons.

With respect to the sequences specified in the method claims, it is clear what function the sequences are required to have. For example, the sequences in claim 2(a)(ii) must bind to the first binding substance in a manner that is similar to or can be compared with the binding of the first binding substance to the corresponding reference sequence as specified in claim 2(a)(i). This is made clear throughout the specification, where the requirements for carrying out the methods of the invention, as reflected in claim 1 and the claims that depend from claim 1, are described. This is also clear in the context of the application as a whole with respect to the claims to agents, corresponding polynucleotide molecules, and related vectors, host cells, and methods (i.e., claims 18 and 21-27). These binding features, when combined with the partial structure information, provide ample written description of the present claims.

Applicants further submit with respect to written description that the specification provides information concerning conserved structures of the peptides of the present claims. For example, in paragraph [0179] of the application publication, it is noted that both ANP and BNP include sequences that form a conserved ring structure in the native molecules, and that a binding

substance of the invention may bind to such structures, in one example of the invention. In addition, paragraph [0181] of the application publication provides several examples of peptides to which binding substances of the invention may bind. Further with respect to this matter, Applicants comment that the activities of the subject sequences under consideration is binding to a binding substance, such as an antibody, as discussed above. This is in contrast to the facts of *Kubin*, where the binding was of variants of a purportedly new protein to another particular protein (CD48). The present facts are different because, as discussed above, when requiring a binding substance to bind to a protein variant, it is generally feasible using standard methods to obtain a binding substance, such as an antibody, that binds to the variant.

Applicants further submit that adequate written description should be found in the present case, as the facts of the present case are similar to (if not better than) those of Example 11B of the Patent Office Written Description Training Materials (Revision 1, March 25, 2008), in which adequate written description was found. In particular, as in Example 11B, the present claims specify percent identity in the context of sequences for which there is knowledge concerning structure and function (with the function being binding to a binding substance, such as an antibody, and also taking into consideration knowledge of the extracellular binding domain of GC-A and conserved regions within proANP and proBNP sequences). Further, the activity of the present claims (binding to a binding substance, such as an antibody), is more readily described than the activity in the example, as different antibodies can be generated to bind to a sequence variant according to the present claims, while in the Example there appears to be a requirement of a binding to a particular ligand (i.e., not to an antibody) or maintenance of enzymatic activity.

Applicants also request that the please Examiner keep in mind when considering this

matter that the present application does not concern the discovery of novel proteins from nature. Rather, the invention relates to new and non-obvious detection methods, which employ substances such as antibodies that bind to known sequences (proANP and proBNP-related sequences) and also a known binding substance (GC-A). ProANP, proBNP, and GC-A have been known for many years, and structural features of these proteins have been extensively characterized. Thus, if one skilled in the art were to wish to consider making a variant for use in the present invention, they could, if desired, consult with years of publications on different features of these molecules. Such action is not required to carry out the invention, however, as any variant falling within the scope of a claim of the application could readily be tested for desired binding properties, as discussed above.

In view of the above, it is clear that the present inventors were in possession of the claimed invention at the time of filing and, thus, that the invention is adequately described. Applicants therefore request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 16, and 17 were rejected under 35 U.S.C. § 103(a) for obviousness over Clerico et al., J. Endoc. Invest. 21:170-179, 1998, in view of Clerico et al., Clin. Chemistry 46:1529-1534, 2000. Applicants request that this rejection be reconsidered and withdrawn.

Before addressing the cited references, Applicants would first like to make clear that a central feature of the present invention is the detection of *both* proANP and proBNP-related sequences at the *same time*, in the *same test reaction*, yielding a *single test result*. This is what was meant in original claim 1 by "simultaneous" detection, and this concept has been further emphasized by amendment of claim 1 to state that the simultaneous detection achieved by the

method of claim 1 is carried out in a single assay. Such an approach, which provides substantial benefits with respect to ease of use and efficiency, is not taught or suggested in the cited references.

Claim 1 thus is drawn to an *in vitro* method for determining activation or inactivation of ANP and BNP hormonal systems in a subject, by simultaneously detecting in a single assay the presence or amount of ANP and BNP prohormones or fragments thereof in a sample from the subject. Claim 16 specifies that the method of claim 1 is an immunoassay, and claim 17 specifies that the method of claim 1 is diagnostic of heart failure or monitors treatment of a cardiac condition.

Clerico (1998) was cited for teaching the measurement of plasma ANP and BNP in patients with heart failure, to monitor their conditions. As described in Clerico (1998), the detection of ANP and BNP is carried out in separate reactions, using separate test kits (see pages 172 and 173). The Examiner states in the rejection that the polypeptides (ANP and BNP) were tested from the same subject and, absent evidence to the contrary, the measurements would constitute simultaneous detection. Clerico (2000) was cited for teaching that cardiac natriuretic hormones are a family of related peptides, including ANP, BNP, and N-terminal portions of proANP and proBNP, which may be present in greater amounts in plasma than ANP and BNP. The Examiner concludes that it would have been obvious to use the methods of Clerico (1998) to detect the different natriuretic protein forms taught by Clerico (2000), particularly in view of the teaching of Clerico (2000) of the higher concentrations of these forms in plasma.

In response to this rejection, Applicants submit that, regardless of whether the tests of Clerico (1998) were carried out at the same time, they were clearly carried out in separate reactions, using separate kits and reagents, and resulting in two sets of results (one for ANP-

related peptides and one for BNP-related peptides). Clerico (2000) similarly provides no teaching or suggestion to carry out detection of proANP and proBNP-related sequences (including the prohormones and N-terminal fragments thereof) in a single reaction, to obtain a single result, which is a central feature of the present invention, as described above. In view of these substantial differences in the methods of the present invention and those of Clerico (1998 and 2000), Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 2-4 and 7-15 were rejected for obviousness over Clerico (1998), in view of Clerico (2000), and further in view of Buechler et al., U.S. Patent No. 7,341,838. Applicants request that this rejection be reconsidered and withdrawn for the reasons set forth below.

Claim 2 specifies that the method of claim 1 is carried out using a first specific binding substance that is able to bind to both proANP and proBNP-related sequences, as noted in the claim; claim 3 specifies the use of a first binding substance having the indicated binding characteristics, as well as an agent including proANP and proBNP-related sequences, as noted in the claim; claim 4 specifies that the first binding substance of claim 3 is a bi- or oligo-specific binding substance, or a mixture of mono-specific binding substances; claims 7 and 8 specify that the first binding substance comprises an antibody (or a fragment or derivative thereof); claims 9 and 10 specify sequence information with respect to the agent of claim 3; claim 11 specifies that the agent is a polypeptide; claim 12 specifies that the first binding substance and/or the agent is detectably labeled and/or immobilized; claim 13 specifies the use of a second binding substance; claim 14 specifies that the second binding substance is detectably labeled and/or immobilized; claim 15 specifies that the second binding substance causes precipitation of the first binding substance and any peptide bound thereto; claim 16 specifies that the method of claim 1 is an immunoassay; and claim 17 specifies that the method of claim 1 is diagnostic of heart failure or

monitors treatment of a cardiac condition.

The Clerico references were cited for the reasons discussed above. Buechler ('838) was cited for describing amino acid sequences bearing similarity to SEQ ID NOs:3 and 6, which are stated by Buechler ('838) to correspond to proANP and proBNP. The Examiner states that one of skill in the art would have recognized that antibodies which recognize the sequences of Buechler ('838) would also recognize the sequences of the present claims, and that Buechler ('838) teaches measuring the amounts of ANP and BNP-related fragments by using antibodies, including bivalent antibodies. In view of these teachings, the Examiner concludes that it would have been obvious to modify the methods of Clerico (1998 and 2000) by substituting the sequences taught by Buechler ('838) and utilizing bispecific antibodies, as taught by Buechler ('838). Applicants respectfully disagree and request that this rejection be reconsidered and withdrawn.

As discussed above, a central feature of the present invention is the simultaneous detection of both proANP and proBNP-related sequences in a single assay, to obtain a single result. Also as discussed above, the methods of Clerico involve the use of two separate assays for separate detection of ANP and BNP-related sequences, resulting in more than one result. Buechler ('838) does not add what is missing from the Clerico references in supporting this rejection, as Buechler ('838) does not teach or suggest testing for both proANP and proBNP-related sequences at the same time, in a single assay, to obtain a single result. In view of the above, Applicants request that this rejection be reconsidered and withdrawn.

Claims 5 and 6 were rejected for obviousness over Clerico (1998), in view of Clerico (2000) and Buechler (U.S. Patent No. 7,341,838), and further in view of Bentivegna et al., WO 01/79231. Applicants request that this rejection be reconsidered and withdrawn.

Claim 5 specifies that the first binding substance comprises natriuretic receptor GC-A or a related sequence, while claim 6 specifies that the first binding substance comprises the extracellular binding domain of GC-A.

The Clerico (1998 and 2000) and Buechler ('838) references were cited for the reasons described above. Bentivegna ('231) was cited for teaching a sequence that corresponds to SEQ ID NO:34 of the present application, which is the natriuretic receptor GC-A. The Examiner states that it would have been obvious to modify the methods of Clerico (1998 and 2000) and Buechler ('838), by utilizing the GC-A receptor, which binds to both ANP and BNP, in place of antibodies against these proteins. Applicants respectfully request that this rejection be reconsidered and withdrawn for the reasons provided above with respect to the prior rejections for obviousness. In particular, none of the cited references, alone or in combination, provide any teaching or suggestion of a central feature of the present invention, which is the simultaneous detection of both proANP and proBNP-related sequences in a single assay, giving rise to a single result. Rather, in carrying out methods according to the cited references, one skilled in the art would test for proANP and proBNP-related sequences individually, in separate reactions, resulting in more than a single test result. In view of this, Applicants ask that this rejection be withdrawn.

Claims 18-22 and 38 were rejected for obviousness over Nakata et al., EP 1118329, 2001, in view of Buechler, U.S. Patent No. 7,341,838. Applicants request that this rejection be reconsidered and withdrawn, for the following reasons.

Claim 18 specifies an agent comprising both proANP and proBNP-related sequences, as set forth in sections (i)-(iii) of parts (a) and (b) of the claim, respectively. As discussed above, the proANP and proBNP-related sequences in the agent are part of the same molecule (see

paragraphs [0218] – [0238] of the application publication). Dependent claims 19-22 specify that the agent of claim 18 includes particular sequences (claims 19 and 20), is labeled with a detectable label (claim 21), or is a polypeptide agent (claim 22). Claim 38 has been canceled.

Nakata ('329) was cited for teaching compositions including ANP and BNP-related sequences such as α-ANP, α-ANP [4-28], α-ANP [5-28], BNP-26, BNP-32, and BNP-45, as well as certain ANP and BNP-related dimer and high molecular weight structures, and Buechler ('838) was cited for teaching certain ANP and BNP prohormone-related sequences. The Examiner states that it would have been obvious to substitute the sequences of Nakata ('329) with those of Buechler ('838), and that it would have been obvious to one of skill in the art to make a fusion protein, "so that one could have a protein comprising equimolar amounts of pro-BNP and pro-ANP to use as a standard in immunoassays using bivalent antibodies (as disclosed by the '838 patent) to detect both proteins."

Applicants respectfully disagree with this rejection, as there is no teaching or suggestion in the cited references to make fusion proteins or other molecules including both proANP and proBNP-related sequences, as is required by the present claims. Such a teaching or motivation certainly does not come from Nakata ('329), which does not mention fusion proteins or immunoassays at all. As to Buechler ('838), the focus of this patent is detection of natriuretic protein peptides and fragments, with a focus on BNP. Bucchler ('838) nowhere mentions detection of both proANP and proBNP-related sequences in an assay, and provides no teaching or suggestion for using fusion proteins including proANP and proBNP-related sequences. Buechler ('838) does mention bivalent antibodies, but only in a general listing of different types of antibodies, and certainly with no indication that such antibodies should detect both proANP and proBNP-related sequences. Thus, there is no teaching or suggestion of detecting both

proANP and proBNP-related sequences in the cited references, and there is also no teaching or suggestion to make the fusion proteins noted by the Examiner. Applicants therefore request reconsideration and withdrawal of this rejection.

Claims 23-27 were rejected for obviousness over Lewicki et al., U.S. Patent No. 5,212,286 and Simari, WO 00/71576. Applicants request that this rejection be reconsidered and withdrawn.

Claim 23 specifies a polynucleotide sequence encoding a polypeptide agent as defined in claim 18, or the complement thereof; claim 24 specifies a polynucleotide according to claim 23, in reference to particular sequence identifiers; claim 25 specifies an expression vector comprising a polynucleotide according to claim 23; claim 26 specifies a host cell comprising such a polynucleotide; and claim 27 specifies a method for making a polypeptide of claim 22 by cultivating a host cell comprising a polynucleotide as specified in claim 23, and recovering the expressed polypeptide.

Lewicki ('286) was cited for teaching a sequence encoding an ANP, while Simari ('576) was cited for teaching a sequence encoding a BNP, as well as "that compounds of the disclosed invention (polypeptides encoded by the disclosed nucleotide sequences) may be mixed with, bonded to or conjugated with compounds having the same or a complementary range of biological activities." The Examiner states that it would have been obvious to combine the teachings of Lewicki ('286) and Simari ('576) to produce the claimed compositions based on the prior-quoted statement, and that "it would be advantageous to have a composition comprising polynucleotides encoding both ANP and BNP in order to efficiently produce said polypeptides recombinantly, since the art teaches both polypeptides having potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects." Applicants respectfully disagree with this

characterization.

The quoted passage from Simari ('576) concerns mixing together or conjugation of *polypeptides*, not polynucleotides. Further, there is no teaching in Simari ('576) that even if proANP and proBNP-related sequences were produced in a fusion protein, from a single polynucleotide, they would have the biological activities noted to be of interest by the Examiner (i.e., potent diuretic, natriuretic, and vascular smooth muscle-relaxing effects). The present claims specify polynucleotide molecules encoding proteins including proANP and proBNP-related sequences, and these proteins can be used in immunoassays to detect levels of proANP and proBNP-related proteins in samples. There is no teaching or suggestion in the Lewicki ('286) and Simari ('576) references of such proteins or polynucleotides encoding them and, thus, this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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